ANIMAL INHALATION TESTS

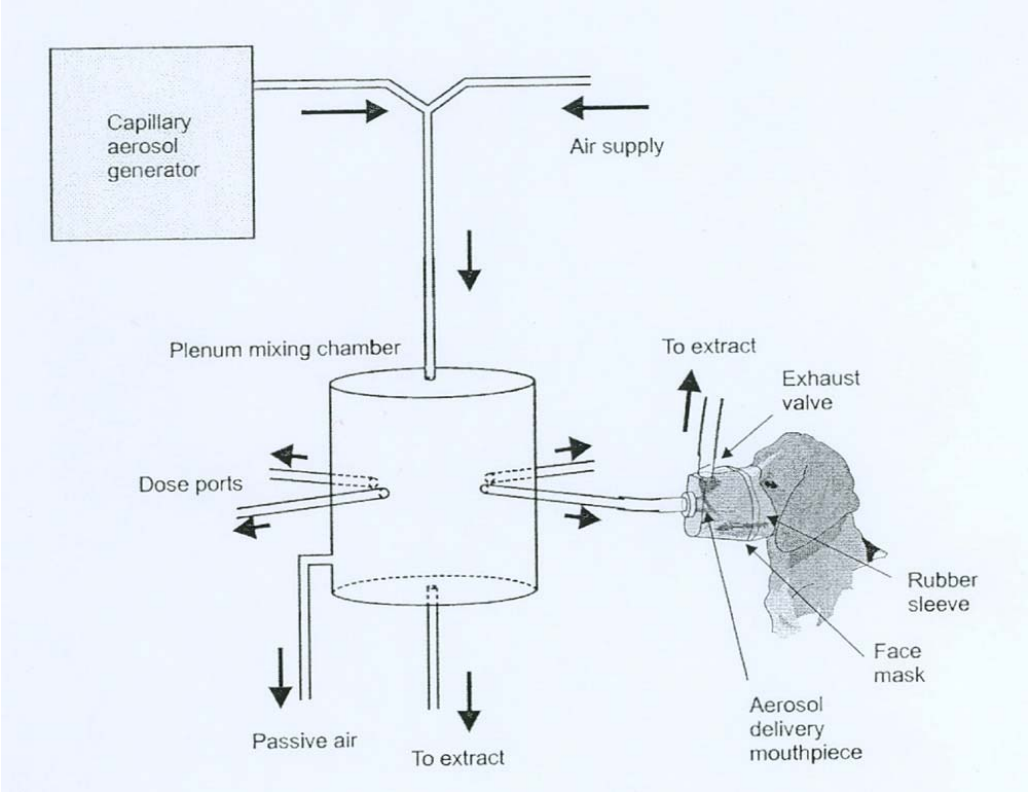


Fig. 1. Diagram of the inhalation exposure system and face mask used to deliver CAG-PG aerosol to Beagle dogs in the MTD and 28-day repeated exposure inhalation study. From: Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Werley, MS*, et al. *Toxicology* 287 (2011) 76– 90. *Altria Client Services, Inc.

From: Contract laboratory investigation.

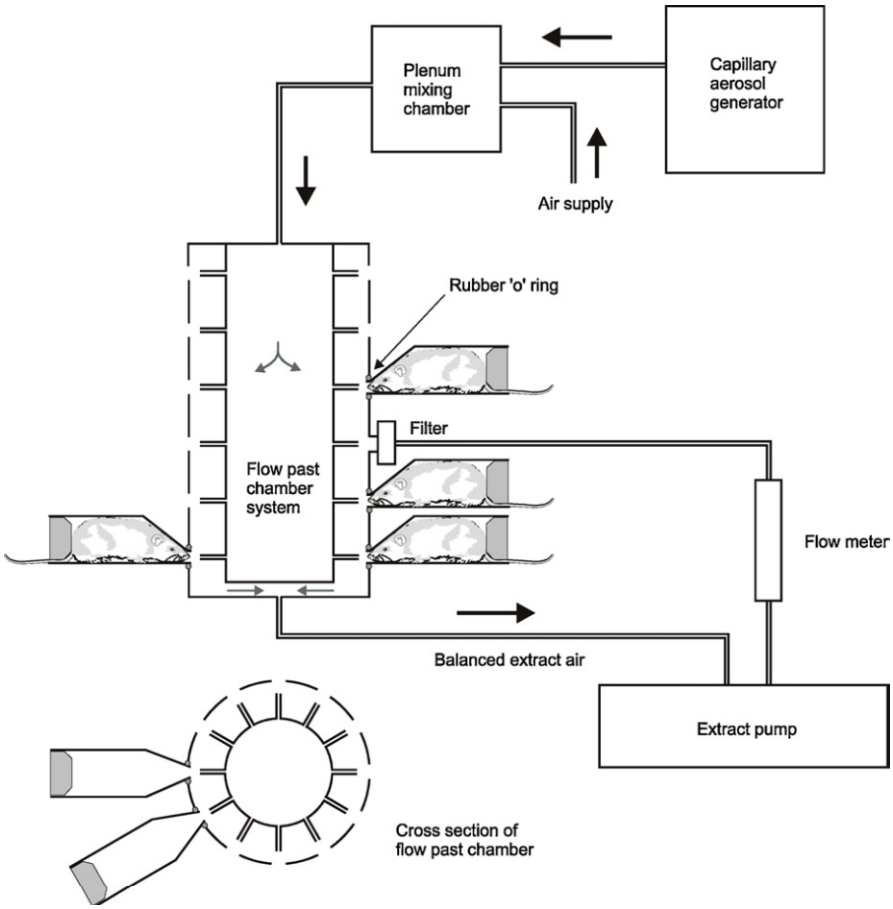
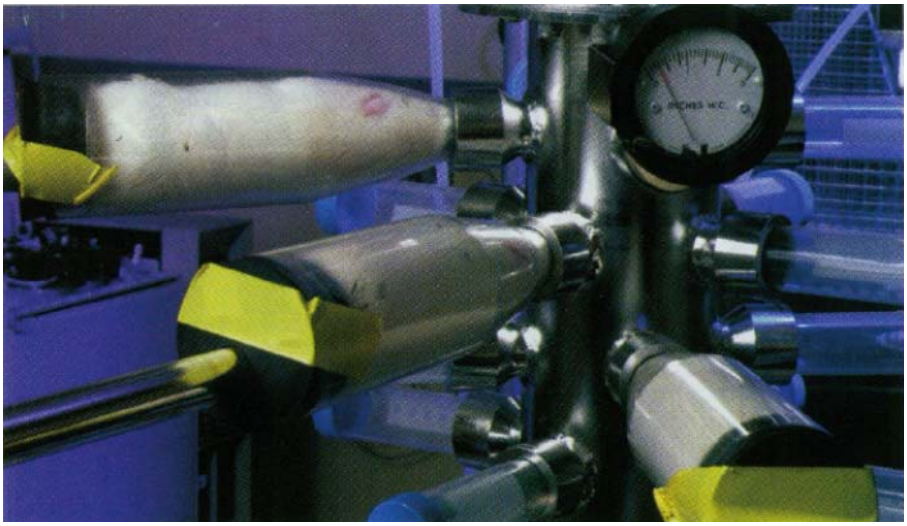


Fig. 2. Diagram of the typical nose-only inhalation exposure system used to deliver PG aerosol to study animals in the acute, 7-day and 28-day repeated exposure studies. From: Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Werley, MS*, et al. *Toxicology* 287 (2011) 76– 90. *Altria Client Services, Inc.



Nose-only studies utilize a tree-like device that delivers vapors directly to the animals' respiratory systems. From: Breathtaking Research, May, M. Environmental Health Perspectives. 2000 Apr; 108(4): A168–A169

PETA AND PCRM
DECEMBER 11, 2015

OUTLINE

1. **PROHIBIT ANIMAL TESTING FOR TOBACCO PRODUCTS**
    a. Animal testing is not required by law
    b. Several European nations prohibit animal testing
    c. Several tobacco companies voluntarily restrict animal testing

2. **RE-ESTIMATE THE BURDEN OF THE PROPOSED COLLECTION OF INFORMATION**
    a. Collection of these animal test data are unnecessary and lack practical utility
    b. *In vitro* methods allow more substances to be tested in less time than *in vivo* methods
    c. FDA's estimate of 27 respondents is surprisingly low

3. **RESTRICT THE USE OF FLAVORS**
    a. Little cigars are cigarettes by definition, so the prohibition on flavors applies
    b. Similar standards are urgently needed for e-cigarettes and other flavored products

4. **PROVIDE CLEAR GUIDANCE**
    a. FDA's guidance to industry is vague and not transparent
    b. FDA should identify a standard battery of *in vitro* tests
    c. Animal tests should require FDA approval following public comments

PROHIBIT ANIMAL TESTING FOR TOBACCO PRODUCTS

UNITED STATES FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT
PUBLIC LAW 111–31—JUNE 22, 2009

SEC. 910. APPLICATION FOR REVIEW OF CERTAIN TOBACCO PRODUCTS.

> (c)(5)(A) … whether permitting a tobacco product to be marketed would be appropriate for the protection of the public health shall… be determined on the basis of well-controlled investigations, which may include 1 or more **clinical investigations**…

SEC. 911. MODIFIED RISK TOBACCO PRODUCTS.

> (l)(1)(A) Such regulations or guidance shall establish minimum standards for scientific studies needed…to show that a substantial reduction in morbidity or mortality among individual tobacco users occurs…
>
> (B) include **validated biomarkers, intermediate clinical endpoints**, and other feasible outcome measures…

INTERNATIONAL PROHIBITIONS ON ANIMAL TESTING FOR TOBACCO PRODUCTS

Belgium, Royal Decree (2008)

Estonia, Animal Protection Act (2003)

Germany, Animal Welfare Act (1998)

Slovakia, Collection on the Protection of Animals (1995)

United Kingdom, Guidance on the Operation of the Animals Act (1986)

TOBACCO COMPANIES WITH POLICIES RESTRICTING ANIMAL TESTING

Imperial Tobacco Group PLC: *We do not commission or conduct research involving animals. We would only undertake animal research if formally required to do so, as instructed by governments or recognised regulatory authorities.*

British American Tobacco PLC: *We prefer not to test our products on animals and currently do not do this routinely. We keep the subject under constant review with the long-term aim of being able to phase it out. We have invested for many years in the development and use of alternative tests.*

RE-ESTIMATE THE BURDEN OF THE PROPOSED COLLECTION OF INFORMATION

DEEMING TOBACCO PRODUCTS TO BE SUBJECT TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT
21 CFR PARTS 1100, 1140, AND 1143

IX. Paperwork Reduction Act of 1995

TABLE 9—ESTIMATED ANNUAL REPORTING BURDEN 1

Activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (in hours)	Total hours
Obtaining an FDA Order Authorizing Marketing of Tobacco Product (the application)					
Cigar Manufacturers (Including Large, Small, and Import- ers)	**1**	1	1	**5,000**	5,000
.....	**1**	1	1	**5,000**	5,000
Pipe Tobacco Manufacturers (Including Importers)	**25**	1	25	**5,000**	125,000
..... Other Tobacco, E-Cigarettes, and Nicotine Product Manu- facturers					
Total Hours Obtaining an FDA order authorizing mar- keting of tobacco product (the application)	.....	.....	.....	.....	**135,000**

RESTRICT THE USE OF FLAVORS

UNITED STATES FAMILY SMOKING PREVENTION AND TOBACCO CONTROL ACT
PUBLIC LAW 111–31—JUNE 22, 2009

SEC. 907. TOBACCO PRODUCT STANDARDS.

(a)(1)(A) … a cigarette… shall not contain…an artificial or natural flavor (other than tobacco or menthol)…

(3)(A) … The Secretary may adopt tobacco product standards in addition to those in paragraph (1) if… appropriate for the protection of the public health.

FEDERAL CIGARETTE LABELING AND ADVERTISING ACT OF 1966

§ 1332. DEFINITIONS

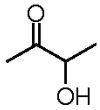
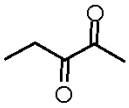
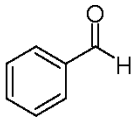
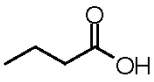
(1) The term "cigarette" means –

(A) any roll of tobacco wrapped in paper or in any substance not containing tobacco, and

(B) any roll of tobacco wrapped in any substance containing tobacco which… is likely to be offered to, or purchased by, consumers as a cigarette described in subparagraph (A).

RESPIRATORY HEALTH AND SAFETY IN THE FLAVOR MANUFACTURING WORKPLACE
FLAVOR MANUFACTURING AND EXTRACT MANUFACTURERS ASSOCIATION, 2012

TABLE 1

FEMA	CAS	Principal Name	Molecular Weight	Calculated Vapor Pressure Value	PEL Data[a,b]	Reported Poundage[c] (lbs)
High Priority						
2003	75-07-0	Acetaldehyde 	44.05	759 mm Hg 20 °C 910 mm Hg 25 °C	OSHA PEL - TWA 200 ppm, 360 mg/m3	1995: 321,000 2005: 70,200 2010: 59,000
2006	64-19-7	Acetic acid 	60.05	12.9 mm Hg 20 °C 17.2 mm Hg 25 °C	OSHA PEL - TWA 10 ppm, 25 mg/m3	1995: 310,000 2005: 271,000 2010: 373,000
2008	513-86-0	Acetoin 	88.11	1.36 mm Hg 20 °C 2 mm Hg 25 °C	NA	1995: 116,000 2005: 133,000 2010: 150,000
2841	600-14-6	2,3-Pentanedione 	100.12	23.8 mm Hg 20 °C 31.1 mm Hg 25 °C	NIOSH REL- TWA 9.3 ppb NIOSH STEL 31 ppb	1995: 2,600 2005: 4,590 2010: 38,000
2127	100-52-7	Benzaldehyde 	106.13	0.705 mm Hg 20 °C 1.01 mm Hg 25 °C	NA	1995: 603,000 2005: 1,410,000 2010: 578,000
2221	107-92-6	Butyric Acid 	88.11	1.5 mm Hg 20 °C 2.11 mm Hg 25 °C	NA	1995: 180,000 2005: 130,000 2010: 229,000

It is recommended that… any compounded flavors… containing any flavoring substances listed in Table 1 in any concentrations if the compounded flavor or any of its individual flavoring substances will be heated during processing… bear a label using the language described below, or language that conveys a similar warning.

WARNING – This flavor may pose an inhalation hazard if improperly handled. Please contact your work-place safety officer before opening and handling, and read the MSDS. Handling of this flavor that results in inhalation of fumes, especially if the flavor is heated, may cause severe adverse health effects.

PROVIDE CLEAR GUIDANCE

APPLICATIONS FOR PREMARKET REVIEW OF NEW TOBACCO PRODUCTS
DRAFT GUIDANCE

Nonclinical Studies

You should generate data to evaluate [toxicity, abuse liability, and carcinogenicity] using **some combination of *in vitro, in vivo,* and/or *ex vivo* studies**.

SCIENTIFIC STANDARDS FOR STUDIES ON MODIFIED RISK TOBACCO PRODUCTS
INSTITUTE OF MEDICINE, 2012

… it is not possible to make laboratory animals use tobacco products the way humans do, and there arE inherent interspecies differences that prevent meaningful extrapolation of human effects…

The number of animal studies required …could potentially be reduced by setting composition standards or limits…

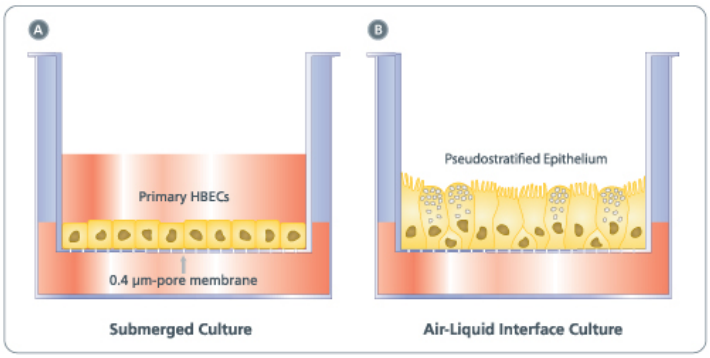
Recommendation 2: The FDA should establish guidance that conveys an expected sequencing of studies, such that preclinical work is completed and submitted to the FDA before clinical (human subjects) work commences…

Evaluation of products *in vitro* should precede *in vivo* assays…

In vitro assays for cytotoxicity, genotoxicity, apoptosis and cell proliferation, oxidative stress, inflammation, mucus production, and endothelial activation are a standard step in evaluations of all… products.

NONANIMAL INHALATION TESTS

AIR-LIQUID INTERFACE



Bérubé K, et al. Toxicology 278(3): 311-8, 2010

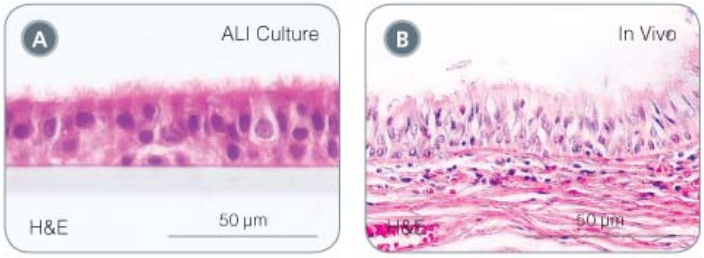


Figure 1. Human Bronchial Epithelial Cells Cultured at the Air-Liquid Interface Recapitulate the In Vivo Bronchial Epithelium. (STEMCELL Technologies)

PRECISION-CUT LUNG SLICES